Medication-related adverse events in patients with cancer and discrepancies in cystatin C- versus creatinine-based eGFR

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Abstract

Background: Creatinine-based estimated glomerular filtration rate ($eGFR_{CRE}$) may overestimate kidney function in patients with cancer. Cystatin C-based eGFR ($eGFR_{CYS}$) is an alternative marker of kidney function. We investigated whether patients with an eGFR discrepancy, defined as $eGFR_{CYS}$ >30% lower than the concurrent $eGFR_{CRE}$, had an increased risk of adverse events resulting from renally-cleared medications.

Patients and Methods: We conducted a cohort study of adult patients with cancer who had serum creatinine and cystatin C measured on the same day between May 2010 and January 2022 at two academic cancer centers in Boston, MA. The primary outcome was the incidence of each of the following medication-related adverse events: 1) supratherapeutic vancomycin levels (>30µg/mL); 2) trimethoprim-sulfamethoxazole-related hyperkalemia (>5.5mEq/L); 3) baclofen-induced neurotoxicity; and 4) supratherapeutic digoxin levels (>2.0ng/mL).

Results: 1988 patients with cancer had simultaneous $eGFR_{CYS}$ and $eGFR_{CRE}$. The mean age was 66 years (SD±14), 965 (49%) were female, and 1555 (78%) were non-Hispanic white.

eGFR discrepancy occurred in 579 patients (29%). Patients with eGFR discrepancy were more likely to experience medication-related adverse events compared to those without eGFR discrepancy: vancomycin levels >30μg/mL (24% vs. 10%, p=0.004), trimethoprim-sulfamethoxazole-related hyperkalemia (24% vs. 12%, p=0.013), baclofen-induced neurotoxicity (25% vs. 0%, p=0.13), and supratherapeutic digoxin levels (38% vs. 0%, p=0.03). The adjusted OR for vancomycin levels >30μg/mL was 2.30 (95% CI 1.05 – 5.51, p = 0.047).

Conclusion: Among patients with cancer with simultaneous assessment of $eGFR_{CYS}$ and $eGFR_{CRE}$, medication-related adverse events occur more commonly in those with eGFR discrepancy. These findings underscore the importance of accurate assessment of kidney function and appropriate dosing of renally-cleared medications in patients with cancer.

Conflicts of interest:
S. Gupta reports research support from BTG International and GE Healthcare. She is a member of GlaxoSmithKline's Global Anemia Council, a consultant for Secretome, and president and founder of the American Society of Onconephrology. MES: Reports research funding from Gilead, Merck, EMD Serono, and Angion. She has served as a scientific advisory board member to Mallinckrodt, Travere, and Novartis. DEL reports research support from BioPorto, BTG International, and Metro International Biotech LLC. All remaining authors have no conflict of interest.

Disclaimers:
The results presented in this report have been presented at the American Society of Onconephrology Symposium in a poster format, however they have not been published previously in whole or part.

Running title: eGFR discrepancies in patients with cancer

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Introduction:

Accurate assessment of estimated glomerular filtration rate (eGFR) is key to dosing renally-cleared medications. While the gold standard method for evaluating kidney function is direct measurement of glomerular filtration rate (mGFR) using inulin or chromium-51 labeled ethylenediamine tetra-acetic acid,[1] GFR estimation using serum creatinine is the most commonly used method in both clinical practice and research.[2-4] Creatinine is a byproduct of muscle metabolism that is filtered and secreted by the kidneys. Despite continued improvements of currently available eGFR equations, creatinine-based eGFR remains imprecise and can overestimate kidney function, particularly in patients with sarcopenia.[5, 6] This can lead to inaccurate dosing of medications that require adjustment based on eGFR, such as commonly used antibiotics, muscle relaxants, anti-epileptic drugs, blood thinners, and antiarrhythmic medications.

Cystatin C is a low molecular weight (13K Dalton) protein produced by all nucleated cells. It is freely filtered by the glomerulus and does not undergo reabsorption or secretion.[7] Unlike creatinine, cystatin C is not readily affected by age, sex, muscle mass, or diet, and has been increasingly used as an alternative to creatinine to estimate GFR.[2, 5, 8] A recent, large study in patients with solid tumors demonstrated that using an equation that combines both creatinine and cystatin C is the most accurate way to estimate GFR.[8, 9]

Because cancer is a significant risk factor for sarcopenia,[10] we hypothesized that having a cystatin C-based eGFR ($eGFR_{CYS}$) that is significantly lower than creatinine-based eGFR ($eGFR_{CRE}$) would be common in patients with cancer. Given that patients with cancer are commonly exposed to numerous medications that require dose adjustment by kidney function, we hypothesized that adverse events related to renally-cleared medications would be higher in patients with a large discrepancy between $eGFR_{CYS}$ versus $eGFR_{CRE}$.

Methods:

Patient population

Using Mass General Brigham's centralized data warehouse, the Research Patient Data Registry (RPDR)[11, 12], we identified adult patients with a pre-existing diagnosis of malignancy who had both serum creatinine and cystatin C measurements on the same day between May 2010 and January 2022. $eGFR_{CRE}$ was calculated using the CKD Epidemiology Collaboration (CKD-EPI) 2021 race-free equation,[5] while $eGFR_{CYS}$ was calculated using the CKD Epidemiology Collaboration (CKD-EPI) 2012 race-free equation.[13, 14]

Data collection

The date of the first simultaneous $eGFR_{CRE}$ and $eGFR_{CYS}$ measurement was considered the baseline date. Comorbidities were defined based on diagnosis codes appearing any time prior to the baseline date, and concurrent medication use was defined by active prescription within 1 year prior to the baseline date. Cancer type was determined by the most frequently used cancer-related diagnosis code prior to the baseline. Baseline chronic kidney disease was defined by the 2021 race free CKD-EPI equation that incorporates both serum creatinine and cystatin C [8], and chronic kidney disease was staged per Kidney Disease Improving Global Outcomes (KDIGO) guidelines.[15] Clinical diagnoses of medication adverse events were determined by manual chart review by two investigators; with a third available to resolve disagreement.

Primary exposure

The primary exposure was eGFR discrepancy, defined as $eGFR_{CYS}$ more than 30% lower than the $eGFR_{CRE}$; the reference group consisted of all other patients and included patients whose $eGFR_{CYS}$ was more than 30% greater than $eGFR_{CRE}$ as this would not place patients at risk factor for adverse medication side effects from renally-cleared medications. The

123 30% cut-off was chosen because it is commonly used in clinical studies to define the accuracy
124 of eGFR from measured GFR.[9, 16] We additionally identified a subset of patients with severe
125 eGFR discrepancy, defined as $eGFR_{CYS}$ more than 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS}$ less
126 than 30 mL/min/1.73m^2.
127
128 *Primary outcome: Adverse events related to renally-cleared medications*
129 We examined the risk of selected medication adverse events using detailed chart
130 review. We selected medications (intravenous vancomycin, trimethoprim-sulfamethoxazole,
131 baclofen, and digoxin) that are typically dose-adjusted based on eGFR and whose side effects
132 could be quantified by drug level monitoring, laboratory abnormalities, or identified by chart
133 review. In all cases, we evaluated drug exposures that occurred within 90 days of the baseline
134 date.
135 The therapeutic range for a vancomycin trough level is 15-20μg/mL and levels greater
136 than 20μg/mL are considered supratherapeutic[17, 18]. We defined severely elevated vancomycin
137 trough levels as those greater than >30 μg/mL and used manual chart review to exclude peak
138 values.[19-21]
139 Trimethoprim-sulfamethoxazole-related hyperkalemia was defined as a serum
140 potassium level >5.5mEq/L (Common Terminology Criteria for Adverse events [CTCAE v 4.0]
141 grade 2), and severe hyperkalemia was defined as a level >6.0mEq/L (grade 3) within 30 days
142 of starting trimethoprim-sulfamethoxazole. As a sensitivity analysis, we determined the average
143 rise in potassium after initiation of trimethoprim-sulfamethoxazole and the rate of an absolute
144 increase in serum potassium ≥0.5mEq/L from baseline.
145 Baclofen toxicity was determined by chart review. Baclofen toxicity was defined as
146 altered mental status, myoclonus, seizure, or orthostatic hypotension/dizziness warranting

discontinuation of the medication.[22, 23] An investigator blinded to cystatin C values evaluated all clinical documentation within 90 days of baseline to identify potential cases of baclofen toxicity.

Digoxin toxicity was determined by chart review. An investigator blinded to cystatin C values evaluated all clinical documentation and digoxin levels obtained within 90 days of baseline. Digoxin toxicity was defined as altered mental status, nausea, orthostatic hypotension, or bradycardia attributed to digoxin by the treating team, with a corresponding digoxin trough level above the therapeutic range.[24, 25]

Secondary outcomes

We evaluated eGFR discrepancy and severe eGFR discrepancy as dependent variables and determined which baseline characteristics and laboratory studies were associated with eGFR discrepancy.

We evaluated the effect of eGFR discrepancy on 30-day mortality. Date of simultaneous $eGFR_{CRE}$ and $eGFR_{CYS}$ served as day 0. Patients lost to follow-up within 30 days were censored at their last visit.

Statistical Analysis

We reported baseline characteristics using counts and percentages for categorical variables and means and standard deviations (SD) for normally distributed continuous variables, and median and interquartile range for skewed variables. Logistic regression models were used to examine the association between baseline demographics, comorbidities, medications, laboratory studies, and eGFR discrepancy in a univariable model. Serum albumin and hemoglobin were evaluated in clinically relevant categories shown in **Table 1**. Variables were then selected based on clinical plausibility and information criteria (Akaike and Bayesian) to generate the final multivariable model. The Wald Chi-squared test was used to assess the significance of explanatory variables. The final model was adjusted for age, sex, race, $eGFR_{CRE}$-

$_{CYS}$, BMI, smoking, hypertension, coronary artery disease, diabetes, cirrhosis, malnutrition, thyroid disease, proton pump inhibitor use, diuretic use, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, corticosteroid use, serum albumin, and hemoglobin,

Chi-squared or Fisher's exact tests were used to assess differences in the rate of medication adverse events across groups, as appropriate. As a sensitivity analysis, we performed univariable and multivariable logistic regression to predict the odds of elevated vancomycin level >30 μg/mL; the final multivariable model was adjusted for age, sex, race, baseline $eGFR_{CRE\text{-}CYS}$, BMI, diabetes, and corticosteroid use. All comparisons were two-sided, with $p<0.05$ considered significant. Kaplan-Meier survival curves and multivariable Cox regression models were used to compare 30-day survival across groups. The final multivariable model was adjusted for age, sex, race, baseline $eGFR_{CRE\text{-}CYS}$, BMI, coronary artery disease, diabetes, cirrhosis, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use, proton pump inhibitor use, diuretic use, corticosteroid use, serum albumin, and hemoglobin level. All analyses were performed using R 4.1.1 (R Foundation), SAS 9.4 (SAS Institute), and GraphPad PRISM V.9.1.0 (GraphPad Software).

Informed Consent:

The Massachusetts General Brigham Institutional Review Board approved this retrospective study and waived the need for informed consent.

Results:

Baseline characteristics

There were 1988 patients with cancer who had a simultaneous creatinine and cystatin C measured between May 4th, 2010, and January 26th, 2022 (**Figure 1**). Mean age was 66 (SD 14 years), 965 (49%) were female, and 1555 (78%) were non-Hispanic white. Patients with a wide array of cancer types were included (**Supplemental Table 1).**

A total of 579 patients (29%) had an $eGFR_{CYS}$ more than 30% lower than $eGFR_{CRE}$. A scatterplot of $eGFR_{CRE}$ vs. $eGFR_{CYS}$ is shown in **Supplemental Figure 1A** and the distribution of the differences between $eGFR_{CRE}$ and $eGFR_{CYS}$ is shown in **Supplemental Figure 1B.** As noted in the methods, the reference group included patients whose $eGFR_{CYS}$ was within 30% of the $eGFR_{CRE}$, as well as the 209 patients (10.5%) whose $eGFR_{CYS}$ was 30% higher than $eGFR_{CRE}$. Predictors of eGFR discrepancy in the multivariable logistic model included white race (adjusted odds ratio [aOR] 1.54, 95% confidence interval [CI] 1.16–2.045, obesity with body-mass-index (BMI) ≥ 30 vs. normal BMI 18.5-24.9 kg/m^2 (aOR 1.51, 95% CI 1.07–2.13), cirrhosis (aOR 1.82, 95% CI 1.14–2.95), diuretic use (aOR 1.68, 95% CI 1.23–2.30), recent corticosteroid use (aOR 1.70, 95% CI 1.28–2.24), hypoalbuminemia (aOR 5.48, 95% CI 3.84–7.86 for serum albumin < 3.0 vs. ≥4.0 g/dL), and anemia (aOR 2.17, 95% CI 1.55–3.03 for hemoglobin <10.0 vs. ≥ 12.0 g/dL) (**Figure 2, Supplemental Table 2**).

Hypoalbuminemia and anemia were the baseline factors most strongly associated with having an eGFR discrepancy; there was a stepwise increase in the likelihood of eGFR discrepancy as albumin and hemoglobin levels decreased (**Figure 3, Supplemental Figure 2**). Among patients with albumin ≥ 4.0 g/dL only 174/1224 (14%) had an eGFR discrepancy, compared to 198/297 (67%) in patients with albumin < 3.0 g/dL. Among patients with hemoglobin ≥ 12 g/dL only 117/886 (13%) had an eGFR discrepancy, compared to 130/196 (66%) in patients with hemoglobin < 8.0 g/dL.

There were 139 patients (7.0% of the overall cohort) who had severe eGFR discrepancy ($eGFR_{CYS}$ > 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS}$ < 30mL/min/1.73m^2) (**Supplemental Table 3**). Predictors of severe eGFR discrepancy were similar to eGFR discrepancy and are shown in **Supplemental Table 4**. The rate of eGFR discrepancy and severe eGFR discrepancy varied by cancer type (**Supplemental Figure 3**).

Medication-related Adverse Events

Vancomycin

There were 447 patients who received vancomycin within 90 days of the baseline date, of whom 286 (64%) had a vancomycin trough measured (**Figure 1**). Patients with eGFR discrepancy were more likely to have significantly elevated vancomycin trough levels than the reference group: 129 of 193 (67%) vs. 37 of 93 (40%) of the reference group had a vancomycin level above the therapeutic range (P < 0.001); 46 of 193 (24%) vs. 9 of 93 (10%) had trough level >30 μcg/mL (P = 0.004); 15 of 193 (8%) vs. 0 of 93 (0%) had a trough level >40 μcg/mL (P = 0.003) (**Figure 4A**). The rate of elevated vancomycin trough levels was even higher in patients with severe eGFR discrepancy (**Figure 4A).** After adjustment for baseline demographics, comorbidities, and baseline laboratory studies, patients with eGFR discrepancy had a 2.30-fold adjusted OR (95% CI 1.05 – 5.51) of having a significantly elevated vancomycin trough level >30 μg/mL (**Supplemental Table 5**).

Trimethoprim-sulfamethoxazole

There were 280 patients who received trimethoprim-sulfamethoxazole within 90 days of the baseline date. We excluded 30 (11%) who did not have a serum potassium level checked within 30 days of starting trimethoprim-sulfamethoxazole (**Figure 1**). Patients with eGFR discrepancy were more likely to experience hyperkalemia (potassium >5.5mEq/L) after starting

trimethoprim-sulfamethoxazole compared to the reference group 33 of 135 (24%) vs. 14 of 115 (12%), *P* = 0.013 (**Figure 4B**). The rate of trimethoprim-sulfamethoxazole-related hyperkalemia was even greater in patients with severe eGFR discrepancy, affecting 15 of 45 (33%) of patients (*P* = 0.0018) (**Figure 4B**). A similar trend was found when evaluating the rate of grade 3 hyperkalemia (defined by a potassium level > 6.0mEq) (**Figure 4B**).

Baclofen

There were 32 patients newly prescribed baclofen within 90 days of baseline (**Figure 1**). Five of the 20 patients (25%) with eGFR discrepancy developed clinical evidence of baclofen toxicity which prompted discontinuation of the medication compared to none of the 12 patients in the reference group (*P* = 0.13) (**Figure 5A**). Among those with severe eGFR discrepancy, 3 out of 8 (37.5%) developed baclofen toxicity. The most common symptom of baclofen toxicity was somnolence/depressed level of consciousness (3 cases). Two additional patients developed severe orthostatic hypotension.

Digoxin

There were 102 patients who were prescribed digoxin (**Figure 1**), of whom 34 (33%) had at least one digoxin level measured. Out of the 24 patients with eGFR discrepancy, 9 patients (38%) had a digoxin trough level above the therapeutic range (>2.0 ng/mL) compared to none of the 10 patients in the reference group (*P* = 0.034). Two patients (8.3%) were diagnosed with clinical digoxin toxicity, including one who required digoxin immune fab (**Supplemental Table 6**); both patients diagnosed with clinical digoxin toxicity met criteria for severe eGFR discrepancy (**Figure 5B**).

Thirty-day survival

132 patients (7%) died within 30 days and 173 (9%) were lost to follow-up prior to 30 days. There was significantly higher 30-day mortality in patients with eGFR discrepancy compared to the reference group (**Figure 6).** Even after adjustment for age, sex, race, baseline comorbidities, laboratory tests, and medication use, patients with eGFR discrepancy had a 1.97-fold increased hazard of death (95% CI 1.29–3.01), compared to the reference group (**Figure 6, Supplemental Table 7**).

Discussion:

Our study showed that in a cohort of patients with a history of cancer who have concurrent creatinine and cystatin C measurement, almost 1 out of 3 had an $eGFR_{CYS}$ more than 30% lower than $eGFR_{CRE}$. The high rate of eGFR discrepancy in patients with cancer poses a challenge for clinical decision making and signifies an important knowledge gap in appropriate dose adjustment of medications that primarily undergo renal clearance. We found a considerably higher rate of adverse events associated with select renally-cleared medications in patients with eGFR discrepancy compared to our reference group.

Accurate dosing of renally-cleared medications is a challenge in patients with cancer, among whom sarcopenia is common and overestimation of GFR by creatinine-based equations has been a major concern in clinical practice.[10, 26-28] Cystatin C, which is produced by all nucleated cells and is not dependent on diet or muscle mass, has been validated as an alternative marker to estimate kidney function. However, Cystatin C levels may be falsely increased in patients with obesity, inflammation, current smoking, and corticosteroid therapy.[29-32] In 2021, the National Kidney Foundation and the American Society of Nephrology Task Force recommended that clinicians estimate GFR using a combined equation incorporating both cystatin C and serum creatinine.[33] A recent study of 1200 patients with solid tumors who underwent measured GFR found that $eGFR_{CRE}$ overestimated measured GFR, $eGFR_{CYS}$ underestimated measured GFR, and that the most accurate and precise eGFR was obtained using the combined equation incorporating both cystatin C and serum creatinine.[9] We note that risk factors for eGFR underestimation with cystatin C is greater in patients with higher BMI, current and former smokers, low albumin, higher C-reactive protein, and metastatic disease. It is important to note the overlap with the predictors of eGFR discrepancy we identified in this study. Because we lacked measured GFR, we are unable to determine the accuracy of $eGFR_{CRE}$ and $eGFR_{CYS}$, however, we found that when a large eGFR discrepancy exists, patients with cancer are at higher risk of adverse events from renally-cleared medications.

Our study demonstrated a higher rate of supratherapeutic vancomycin levels in patients with eGFR discrepancy. Vancomycin is a very commonly used intravenous antibiotic in hospitalized patients that is predominantly eliminated by the kidney (>90%). Several studies have demonstrated that vancomycin clearance and target trough achievement may be more accurately predicted by $eGFR_{CYS}$ than $eGFR_{CRE}$.[34-38] A previously published quality improvement initiative that included 399 patients found that a vancomycin dosing algorithm using eGFR estimated by both creatinine and cystatin C (N = 135) was more likely to achieve therapeutic vancomycin trough levels (50% vs. 28%, $p< 0.001$) compared to an algorithm using $eGFR_{CRE}$ alone (N = 264).[36] Trimethoprim-sulfamethoxazole is another commonly used antibiotic in the inpatient and outpatient setting. Trimethoprim can have an “amiloride-like” effect by inhibiting potassium secretion in the distal convoluted tubule; patients with impaired kidney function are much more likely to develop clinically significant hyperkalemia when treated with trimethoprim-sulfamethoxazole.[39] Hyperkalemia occurred more commonly in patients with eGFR discrepancy compared to the reference group. Digoxin is a cardiac glycoside medication approved to treat atrial fibrillation and congestive heart failure that has a narrow therapeutic index. Digoxin is cleared by the kidneys and its toxicity is dose dependent. There have been conflicting reports regarding use of creatinine versus cystatin C to predict digoxin clearance.[40-44] Here, we found that patients with eGFR discrepancy were significantly more likely to have supratherapeutic digoxin trough levels compared to the reference group, and both cases of symptomatic digoxin toxicity occurred in patients with eGFR discrepancy. Baclofen is a muscle relaxant that is commonly prescribed in patients with cancer to inhibit the hiccup reflex. Baclofen is primarily eliminated by the kidney. In patients with impaired kidney function, baclofen accumulation can occur after just a single dose, and can lead to profound central nervous system suppression, ranging from encephalopathy, coma, areflexia, hypotension, and cardiac arrest.[45, 46] Our study showed that symptomatic baclofen toxicity is common in patients with eGFR discrepancy (affecting 25% of patients), whereas no events occurred in the reference group, suggesting that

the $eGFR_{CYS}$ should be considered when prescribing baclofen to patients with cancer. To the best of our knowledge, this is the first study to evaluate $eGFR_{CYS}$ and $eGFR_{CRE}$ in patients receiving baclofen. Taken together, our findings suggest that relying on creatinine-based eGFR alone for medication dosing may be inadequate in patients with cancer and highlights the need to consider $eGFR_{CYS}$ as well.

Finally, consistent with prior knowledge that incorporation of cystatin C adds precision to the eGFR equation in patients with malnutrition, sarcopenia, and cirrhosis,[9, 47, 48] we note that hypoalbuminemia and anemia are important predictors of eGFR discrepancy in patients with cancer. It is likely that these laboratory abnormalities that signify chronic illness are associated with cancer-related sarcopenia. Future prospective studies that include measured GFR are needed to validate this finding. In addition, we found that eGFR discrepancy is associated with significantly higher 30-day mortality even after adjustment for demographics, comorbidities, baseline laboratory studies, and medication use. Although higher serum creatinine and cystatin C have each been shown to be associated with increased mortality in multiple clinical settings,[49-54] our finding suggests that discrepancy between creatinine and cystatin C, in addition to the absolute values of either marker, adds further information and potentially serves as an independent predictor of death.

Our study has several limitations. First, cystatin C was only available on select patients, where it has been ordered as a part of routine care. Since cystatin C is not routinely used in clinical practice, our population was likely enriched for patients in whom clinicians suspected an eGFR discrepancy or kidney injury might exist, this likely an overestimate of the rate of eGFR discrepancy in the oncology population in general. However, the selection bias should be balanced between the eGFR discrepancy group and the reference group, which preserves the validity of comparison of medication-related adverse events between the two groups. Second, we only used a one-time assessment of creatinine and cystatin C, which may not reflect a steady state at the time of measurement. Third, we were not able to determine cancer stage

from our dataset, which may be an important non-GFR determinant of cystatin C and creatinine.[55, 56] Fourth, it is possible that clinician knowledge of the $eGFR_{CYS}$ could have influenced medication dosing; however, such practice would have biased our results toward the null. Accordingly, the magnitude of association between eGFR discrepancy and medication-related adverse events that we report here is likely an underestimate. Finally, our study lacks gold standard GFR measurement given the retrospective design; however, comparing adverse outcomes of renally-dosed medications serves as surrogate marker for accuracy of eGFR.

In conclusion, we found that a >30% eGFR discrepancy is common in patients with cancer and is associated with an increase in adverse events related to commonly used, renally-cleared medications. Future prospective studies are needed to improve and personalize the approach to GFR estimation and medication dosing in patients with cancer.

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591
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Table 1. Patient Characteristics

Covariates	Overall N=1988	eGFR discrepancy N=579	Reference group N=1409
Age	66 (14.1)	68 (14.3)	65(14.0)
Female Sex	965 (48.5)	293 (50.6)	672 (47.7)
Race/Ethnicity			
White	1555 (78.2)	467 (80.7)	1088 (77.2)
Black	184 (9.3)	43 (7.4)	141 (10.0)
Hispanic	89 (4.5)	27 (4.7)	62 (4.4)
Asian	72 (3.6)	20 (3.5)	52 (3.7)
Other	88 (4.4)	22 (3.8)	66 (4.7)
Body Mass Index (kg/m^2)			
Underweight (<18.5)	54 (3.6)	25 (6.1)	29 (2.6)
Normal (18.5 - 24.9)	442 (29.4)	126 (30.8)	316 (28.9)
Overweight (25 - 29.9)	515 (34.2)	114 (27.9)	401 (36.6)
Obese (≥30)	493 (32.8)	144 (35.2)	349 (31.9)
Comorbidities			
Hypertension	1600 (80.5)	507 (87.6)	1093 (77.6)
Coronary Artery Disease	987 (49.6)	377 (65.1)	610 (43.3)
Diabetes Mellitus	1008 (50.7)	393 (67.9)	615 (43.6)
Cirrhosis	105 (5.3)	61 (10.5)	44 (3.1)
Human Immunodeficiency Virus	82 (4.1)	20 (3.5)	62 (4.4)
Smoking	806 (40.5)	266 (45.9)	540 (38.3)
Malnutrition	275 (13.8)	97 (16.8)	178 (12.6)
Thyroid disease	503 (25.3)	177 (30.6)	326 (23.1)
Chronic kidney disease			
eGFR 30 - 50 mL/min per 1.72m^2	804 (40.4)	254 (43.9)	550 (39.0)
eGFR < 30 mL/min per 1.73m^2	514 (25.8)	211 (36.5)	303 (21.5)
Medication Use			
ACEi/ARB	1128 (56.7)	345 (59.6)	783 (55.6)
Proton Pump Inhibitors	1291 (64.9)	441 (76.2)	850 (60.3)
Diuretics	1282 (64.5)	474 (81.9)	808 (57.3)
Corticosteroids*	393 (19.8)	207 (35.8)	186 (13.2)
Labs			
Serum Creatinine (mg/dL)	1.62 (1.03)	1.44 (0.75)	1.70 (1.12)
Serum Cystatin C (mg/L)	1.82 (0.97)	2.37 (1.03)	1.59 (0.84)
$eGFR_{CRE-CYS}$ (mL/min per 1.73m^2)	51 (28)	41 (22)	55 (29)
Serum Albumin (g/dL)			
<3.0	297 (15.5)	198 (34.6)	99 (7.4)
3.0-3.49	187 (9.8)	96 (16.8)	91 (6.8)
3.5-3.9	280 (14.6)	111 (19.4)	169 (12.6)
≥4.0	1152 (60.1)	168 (29.3)	984 (73.3)
Blood Urea Nitrogen (mg/dL)			
≤17	501 (25.2)	99 (17.1)	402 (28.6)
17-25	526 (26.5)	107 (18.5)	419 (29.8)
25-39	482 (24.3)	147 (25.4)	335 (23.8)
>39	478 (24.1)	226 (39.0)	252 (17.9)
Hemoglobin (g/dL)			
≤10.0	597 (30.0)	324 (56.0)	273(19.4)
10 -11.9	505 (25.4)	138 (23.8)	367 (26.0)
≥12.0	886 (44.6)	117 (20.2)	769 (54.6)

Table 1. eGFR discrepancy was defined as $eGFR_{CYS}$ more than 30% lower than $eGFR_{CRE}$. Count and percent or mean and standard deviations are shown. Body mass index was missing for 479 participants (24%), serum albumin was missing for 72 participants (3.6%), and hemoglobin was missing for 46 participants (2.3%). The remaining data was complete. Chronic kidney disease was staged using the $eGFR_{CRE-CYS}$. Abbreviations: $eGFR_{CRE-CYS}$ = estimated Glomerular Filtration Rate using creatinine and cystatin C equation, ACEi/ARB = Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker.

Figure 1. Patient flow

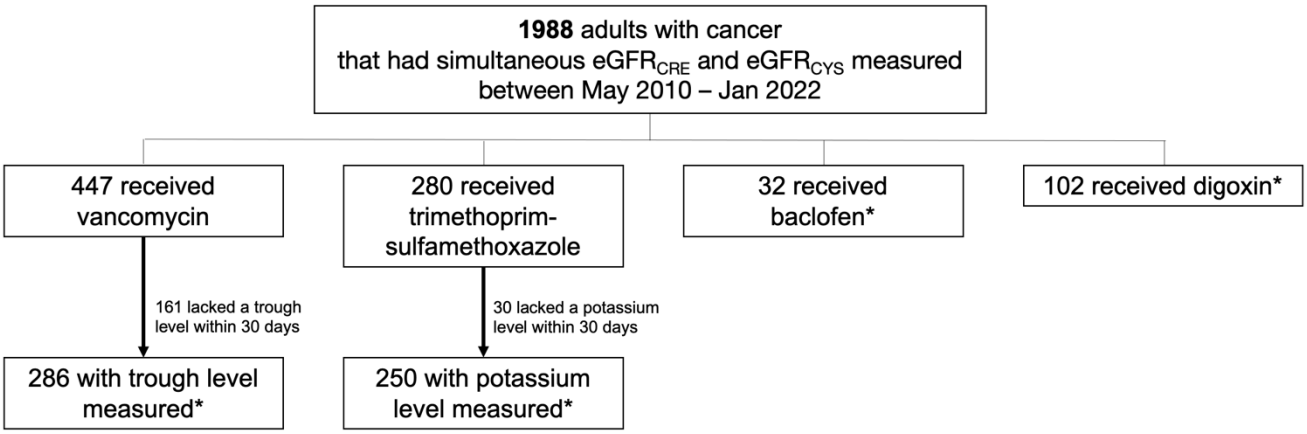
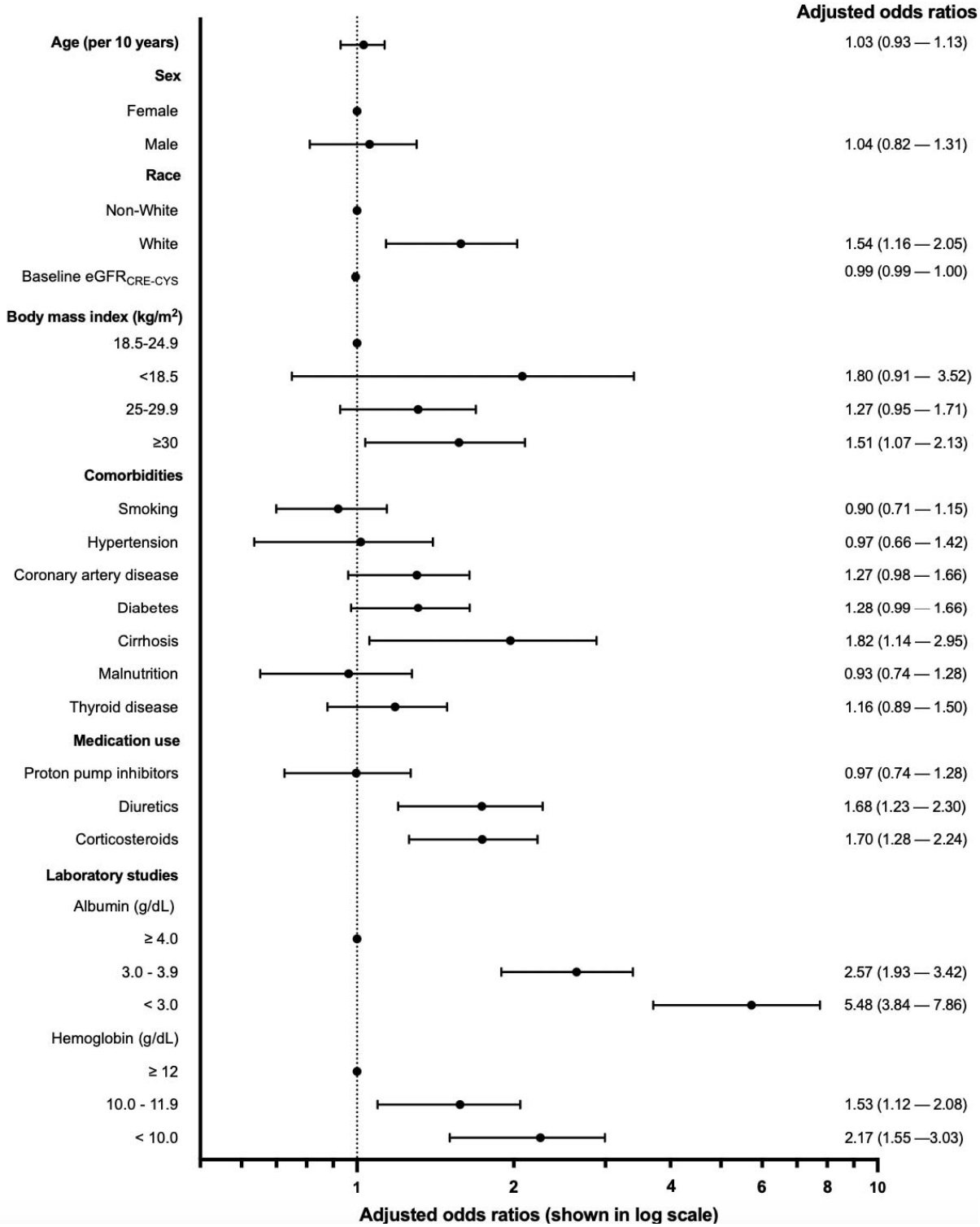


Figure 1. Patient flow. Exposure to each medication was determined by an active prescription within 90 days of the baseline date. *Shows the analyzed sample for each medication. Abbreviations: $eGFR_{CRE}$ = creatinine-based estimated glomerular filtration rate, $eGFR_{CYS}$ = cystatin c-based estimated glomerular filtration rate.

611 **Figure 2. Predictors of eGFR discrepancy**



612
613 **Figure 2. Forrest plot showing adjusted odds ratios.** Logistic regression models were used to
614 estimate the association between baseline characteristics and the eGFR discrepancy ($eGFR_{CYS}$ > 30%
615 lower than $eGFR_{CRE}$) in patients with cancer. The unadjusted and adjusted models are also shown in
616 **Supplemental Table 2.** Abbreviations**:** $eGFR_{CRE-CYS}$ = estimated Glomerular Filtration Rate calculated
617 using the 2021 race-free combined serum creatinine and cystatin C equation

618 **Figure 3. Rate of eGFR discrepancy by albumin and hemoglobin levels**
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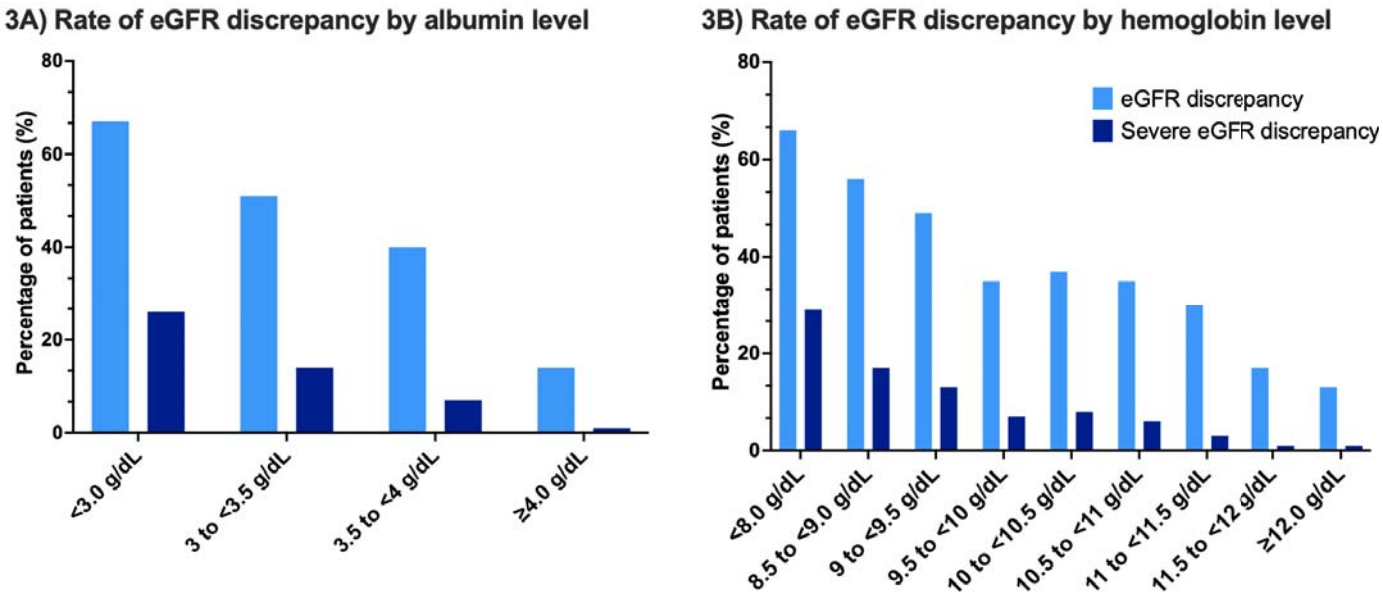

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623 **Figure 3.** eGFR discrepancy defined by $eGFR_{CYS}$ > 30% lower than $eGFR_{CRE}$ shown with light
624 blue bars, and severe eGFR discrepancy ($eGFR_{CYS}$ > 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS}$ <
625 30mL/min/1.73m^2) shown with dark blue bars become more common in patients with worsening
626 hypoalbuminemia (**3A**) and anemia (**3B**).
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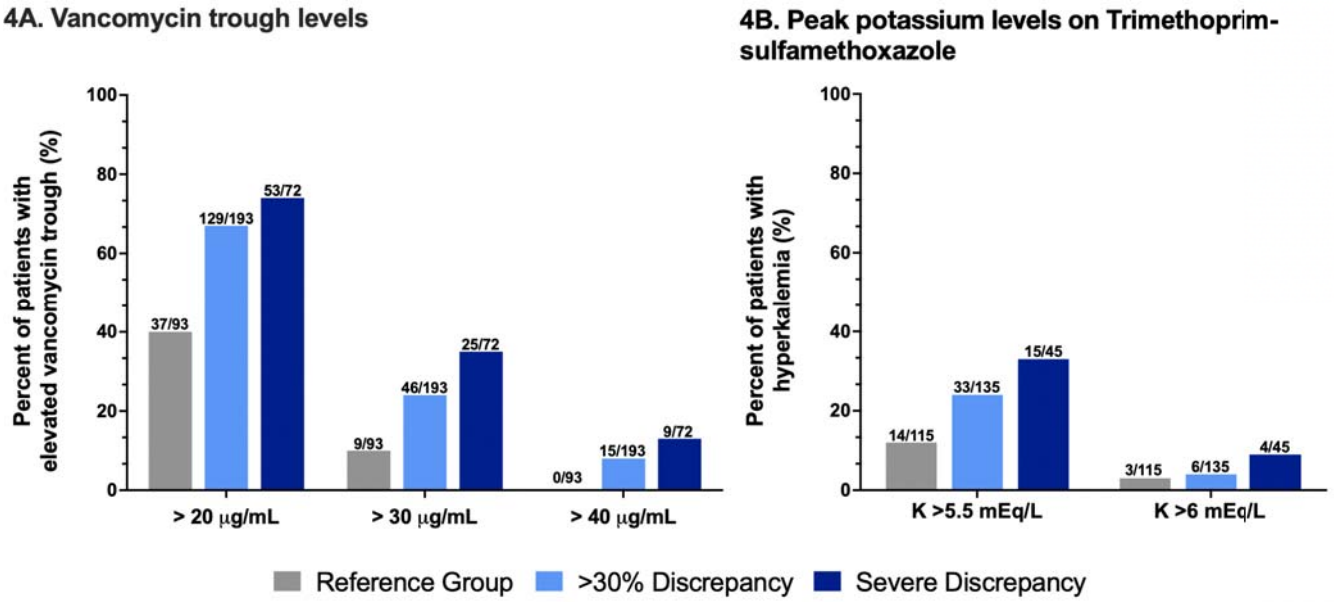
629 **Figure 4. Rate of supratherapeutic vancomycin levels and trimethoprim-**
630 **sulfamethoxazole-related hyperkalemia in patients with eGFR discrepancy**
631



632
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634 **Figure 4A.** Highest trough vancomycin levels obtained within 30 days of starting vancomycin in
635 patients with eGFR discrepancy ($eGFR_{CYS}$ more than 30% lower than $eGFR_{CRE}$), severe eGFR
636 discrepancy ($eGFR_{CYS}$ more than 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS}$ < 30mL/min/1.73m^2),
637 and the reference group. We excluded any vancomycin level obtained less than 6 hours after
638 the last administered vancomycin dose. **Figure 4B.** Rate of Grade 2 or 3 hyperkalemia in
639 patients receiving trimethoprim-sulfamethoxazole.
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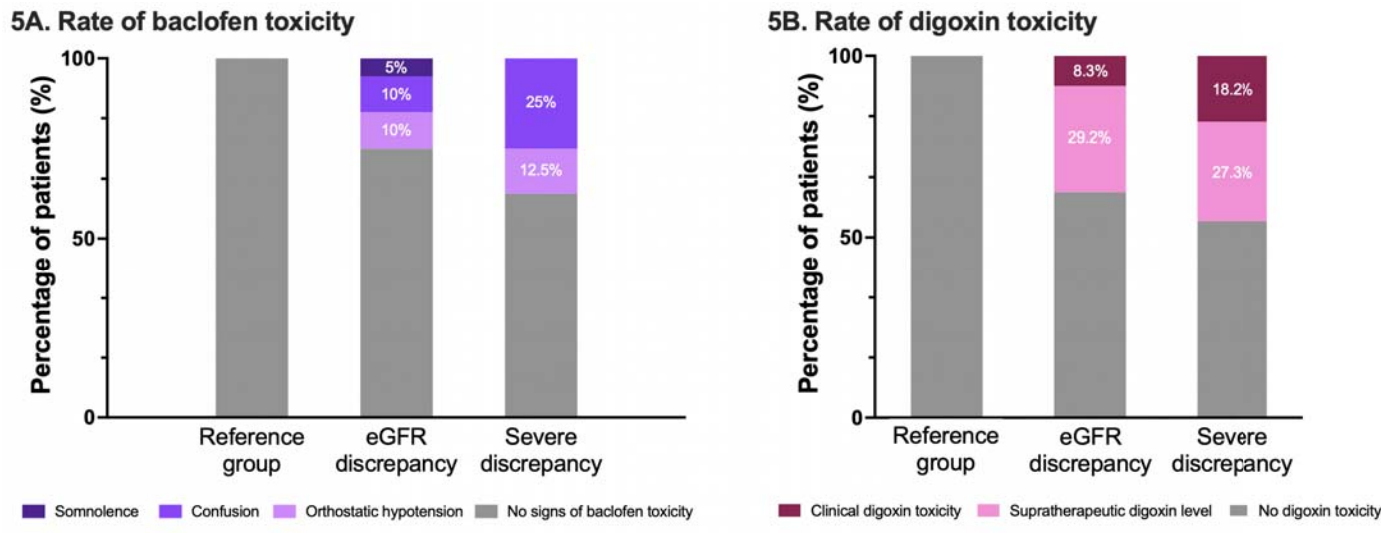
643 **Figure 5. Rate of baclofen toxicity and digoxin toxicity in patients with eGFR discrepancy**
644



645
646
647 **Figure 5A.** Rate of baclofen toxicity in patients with eGFR discrepancy, severe eGFR,
648 discrepancy and the reference group. **Figure 5B.** Rate of supratherapeutic digoxin level defined
649 by >2.0μg/dL. Both cases of clinical digoxin toxicity occurred in patients with severe eGFR
650 discrepancy ($eGFR_{CYS}$ more than 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS}$ < 30mL/min/1.73m^2).
651 There were no cases of supratherapeutic digoxin levels or digoxin toxicity in the reference
652 group.
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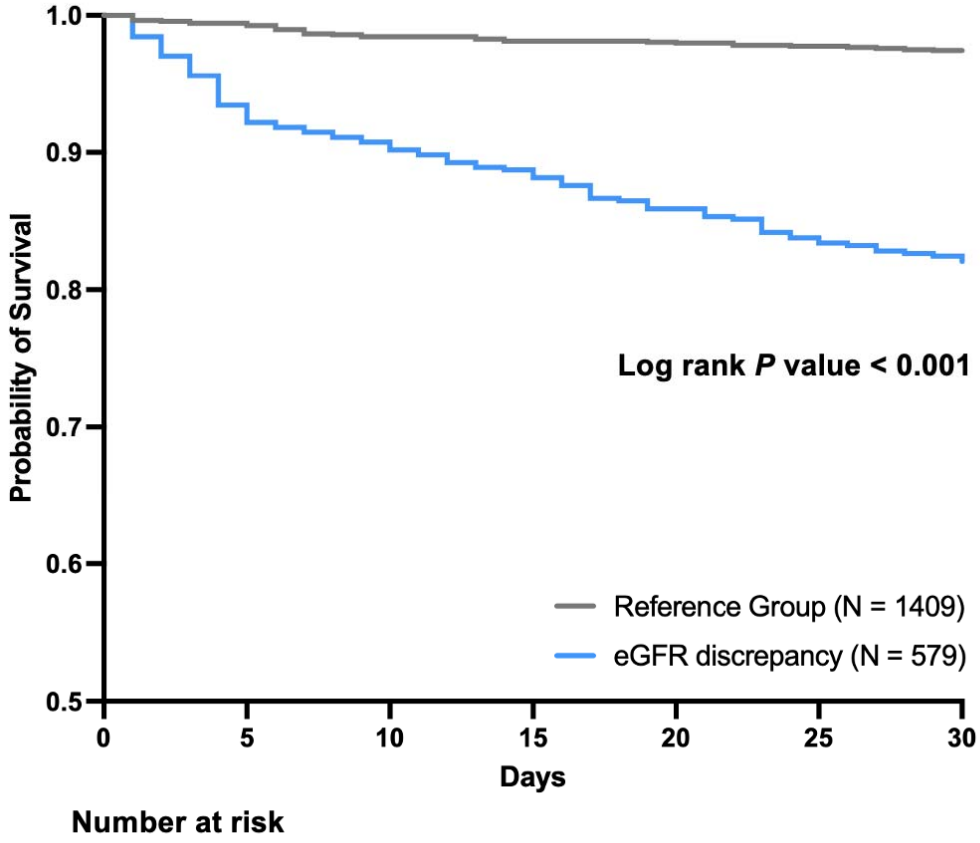
Figure 6. Kaplan-Meier curve of 30-day survival

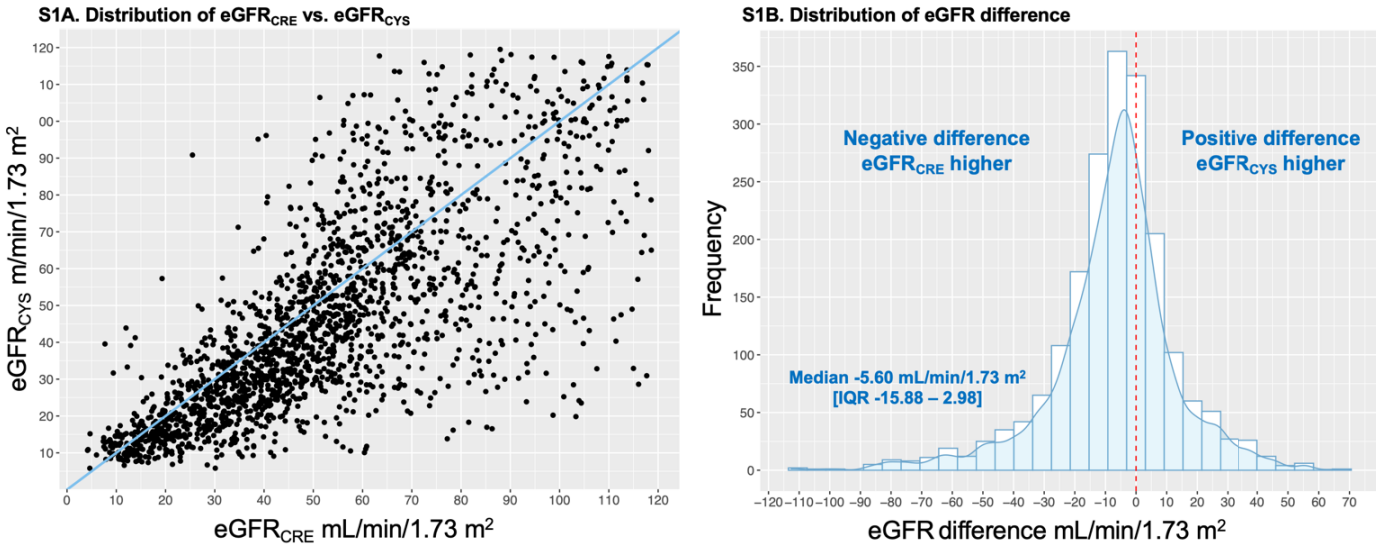


Number at risk

Reference	1409	1318	1300	1285	1280	1270	1262
eGFR discrepancy	579	519	494	474	453	435	425

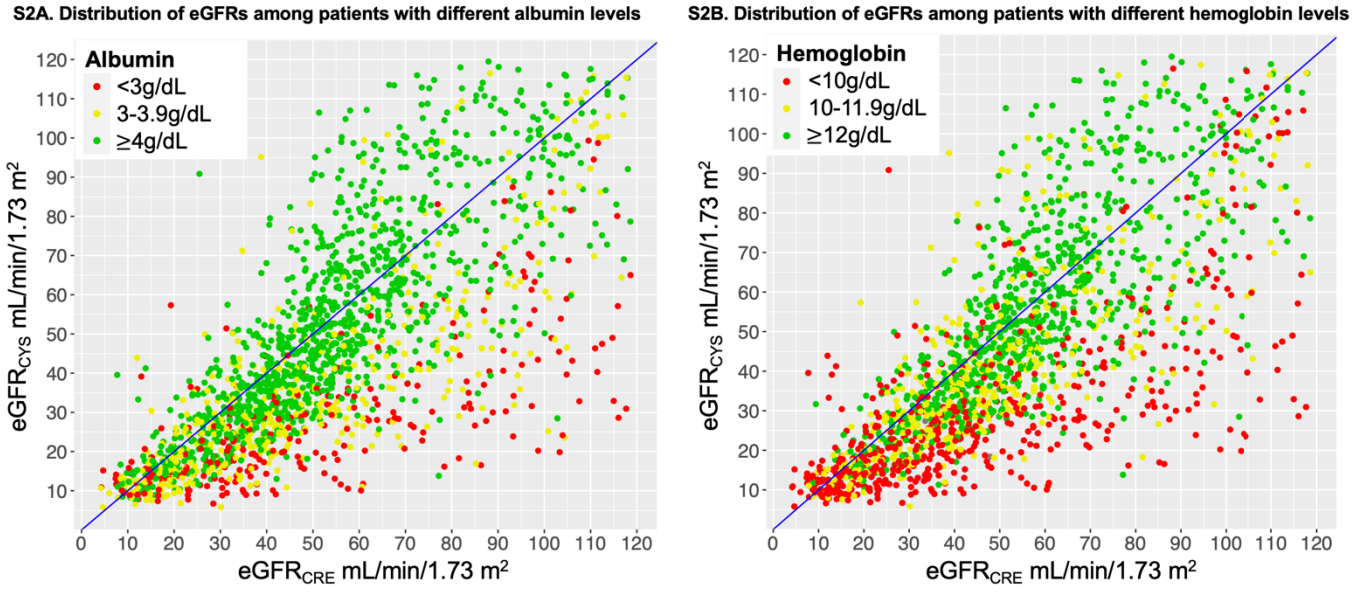
Figure 6. Survival analysis using Kaplan Meier method comparing 30-day survival between reference group and those who had eGFR discrepancy. Unadjusted and adjusted model is shown in Supplemental Table 7.

Supplemental Figure 1. Scatter plot of creatinine-based and cystatin C-based eGFR, and distribution of eGFR difference



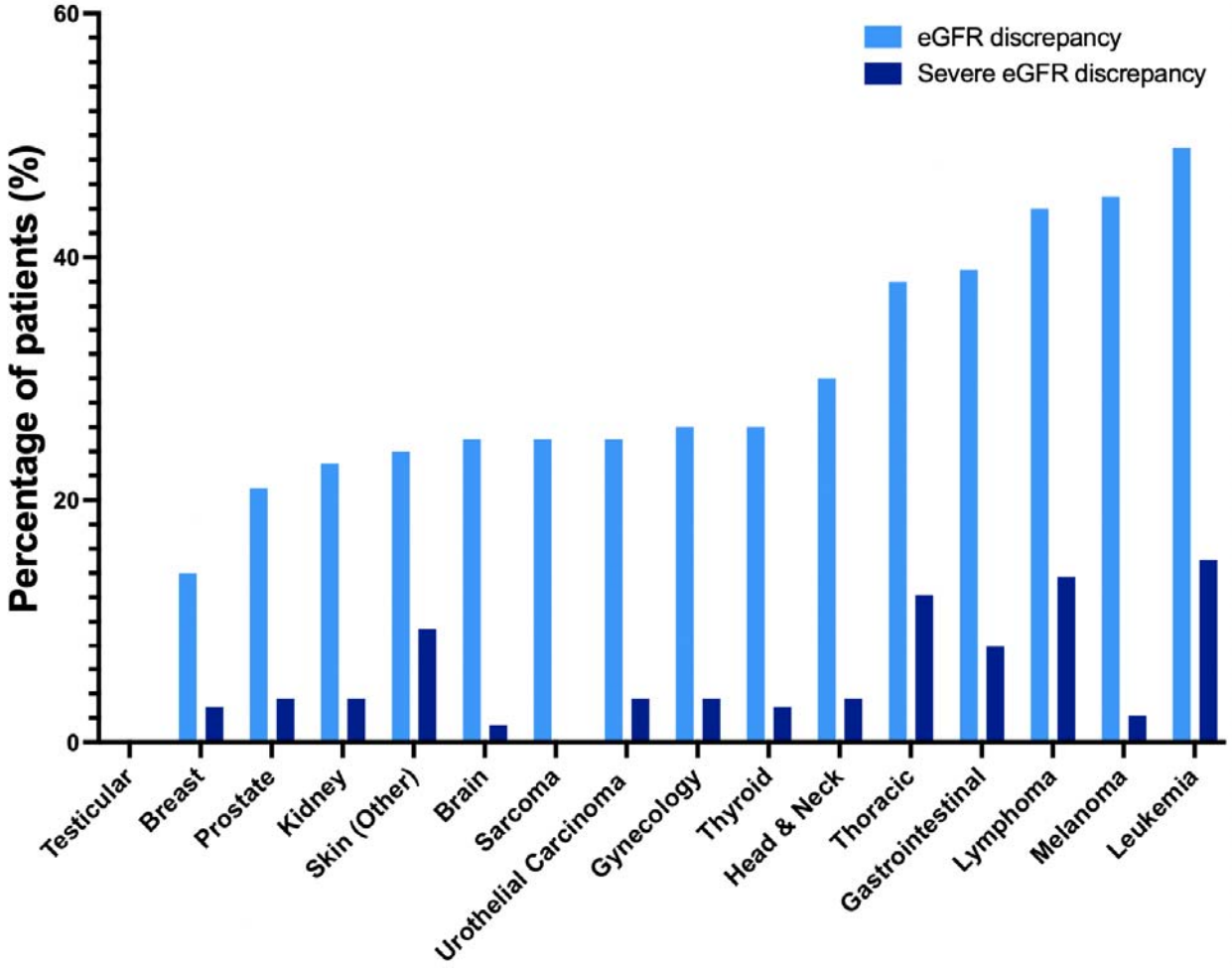
Supplemental Figure 1. Scatterplot showing distribution of eGFR$_{CRE}$ and eGFR$_{CYS}$ among patients with cancer (S1A); the blue line is the line of equality. Figure S1B. A histogram and superimposed density curve showing the distribution of eGFR difference defined by eGFR$_{CYS}$ minus eGFR$_{CRE}$. The red dotted line signifies equivalence between eGFR$_{CRE}$ and eGFR$_{CYS}$.
Abbreviations: IQR, interquartile range

Supplemental Figure 2. Scatter plot of creatinine-based and cystatin C-based eGFR by albumin and hemoglobin levels.



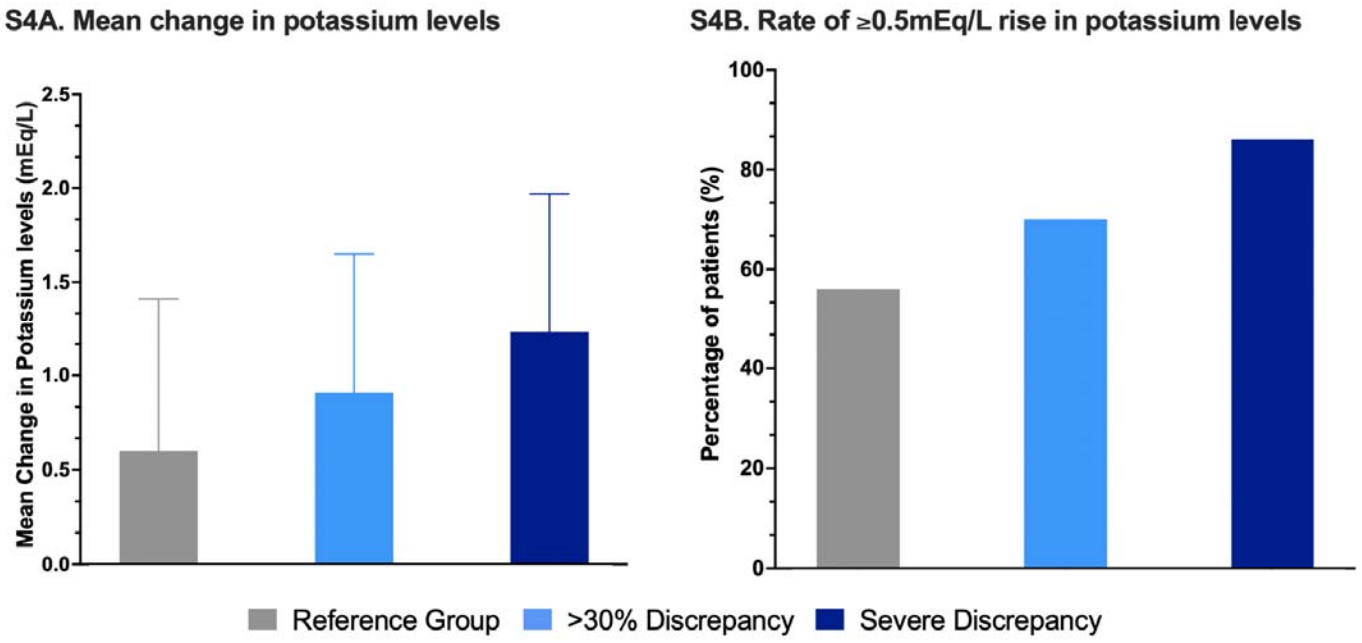
Supplemental Figure 2. Scatterplot showing distribution of eGFRs among patients with cancer stratified by different albumin levels (S2A) and hemoglobin levels (S2B) as shown. The identity line (line of equality) is shown in blue.

Supplemental Figure 3. Rate of eGFR discrepancies by cancer type



Supplemental Figure 3. Rate of eGFR discrepancy and severe eGFR discrepancy by cancer type. eGFR discrepancy is defined by an $eGFR_{CYS}$ more than 30% lower than $eGFR_{CRE}$. Severe eGFR discrepancy was defined as an $eGFR_{CYS}$ more than 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS} < 30 mL/min/1.73m^2$.

713 **Supplemental Figure 4**. Changes in potassium levels among patients who received
714 trimethoprim-sulfamethoxazole.
715



716
717
718 **Supplemental Figure S4A.** Mean change in potassium levels with standard deviations among
719 trimethoprim-sulfamethoxazole recipients; error bars show standard deviation. **S4B**. Rate of
720 ≥0.5mEq/L rise in potassium levels among trimethoprim-sulfamethoxazole recipients. eGFR
721 discrepancy is defined by an $eGFR_{CYS}$ more than 30% lower than $eGFR_{CRE}$. Severe eGFR
722 discrepancy was defined as an $eGFR_{CYS}$ more than 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS}$ <
723 30mL/min/1.73m^2.
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728 **Supplemental Table 1. Cancer type**
729

	Overall	eGFR discrepancy	Reference group
	N=1988	N=579	N=1409
Cancer types*			
Urothelial	92 (4.6)	23 (4.0)	69 (4.9)
Brain	40 (2.0)	10 (1.7)	30 (2.1)
Breast	228 (11.5)	32 (5.5)	196 (13.9)
Gastrointestinal	177 (8.9)	69 (11.9)	108 (7.7)
Gynecologic	141 (7.1)	36 (6.2)	105 (7.5)
Head & Neck	50 (2.5)	15 (2.6)	35 (2.5)
Leukemia	129 (6.5)	63 (10.9)	66 (4.7)
Lymphoma	123 (6.2)	54 (9.3)	69 (4.9)
Melanoma	29 (1.5)	13 (2.2)	16 (1.1)
Prostate	147 (7.4)	31 (5.4)	116 (8.2)
Kidney	162 (8.1)	37 (6.4)	125 (8.9)
Sarcoma	4 (0.2)	1 (0.2)	3 (0.2)
Testicular	1 (0.1)	0 (0.0)	1 (0.1)
Thoracic	114 (5.7)	43 (7.4)	71 (5.0)
Thyroid	43 (2.2)	11 (1.9)	32 (2.3)
Skin (Other)	298 (15.0)	71 (12.3)	227 (16.1)

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732 **Supplemental Table 1**. Cancer type was determined by the most commonly appearing cancer-
733 related diagnosis code prior to the baseline date. eGFR discrepancy is defined by an $eGFR_{CYS}$
734 more than 30% lower than $eGFR_{CRE}$.
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Supplemental Table 2. Predictors of $eGFR_{CYS}$ more than 30% lower than $eGFR_{CRE}$

	$eGFR_{CYS}$ >30% lower than $eGFR_{CRE}$					
	Univariable			Multivariable		
Covariates	**OR**	**95% CI**	**p-value**	**Adj OR**	**95% CI**	**p-value**
Age (per 10 years)	**1.12**	**1.05, 1.20**	**0.001**	1.03	0.93, 1.13	0.60
Male Sex	1.12	0.93, 1.36	0.24	1.04	0.82, 1.31	0.77
White Race	1.23	0.97, 1.57	0.092	1.54	0.16, 2.05	**0.003**
Body mass index						
Normal (18.5 - 24.9)	REF	—		—	—	
Under weight (<18.5)	**2.15**	**1.21, 3.81**	**0.009**	1.80	0.91, 3.52	0.087
Overweight (25 - 29.9)	0.99	0.77, 1.27	0.918	1.29	0.95, 1.71	0.113
Obese (≥ 30)	1.03	0.78, 1.36	0.846	**1.51**	**1.07, 2.13**	**0.018**
Smoking	**1.37**	**1.12, 1.66**	**0.002**	0.90	0.71, 1.15	0.40
Comorbidities						
Hypertension	**2.04**	**1.55, 2.70**	**<0.001**	0.97	0.66, 1.42	0.87
Coronary Artery Disease	**2.44**	**2.00, 2.99**	**<0.001**	1.27	0.98, 1.66	0.075
Diabetes Mellitus	**2.73**	**2.23, 3.35**	**<0.001**	1.28	0.99, 1.66	0.064
Cirrhosis	**3.65**	**2.45, 5.48**	**<0.001**	**1.82**	**1.14, 2.95**	**0.013**
Human Immunodeficiency Virus	0.78	0.45, 1.28	0.336			
Malnutrition	**1.39**	**1.06, 1.82**	**0.016**	0.93	0.67, 1.29	0.69
Thyroid disease	**1.46**	**1.18, 1.81**	**<0.001**	1.16	0.89, 1.50	0.27
Medication Use*						
ACEi/ARB	1.18	0.97, 1.44	0.101			
Proton Pump Inhibitors	**2.10**	**1.69, 2.62**	**<0.001**	0.97	0.74, 1.28	0.83
Diuretics	**3.36**	**2.66, 4.27**	**<0.001**	**1.68**	**1.23, 2.30**	**0.001**
Corticosteroids	**3.66**	**2.91, 4.61**	**<0.001**	**1.70**	**1.28, 2.24**	**<0.001**
Labs						
$eGFR_{CRE-CYS}$	0.98	0.98, 0.98	**<0.001**	0.99	0.99, 1.00	**0.003**
Albumin (g/dL)						
≥4.0	REF	—		—	—	
3.0 to <4.0	**4.8**	**3.77, 6.13**	**<0.001**	**2.557**	**1.93, 3.42**	**<0.001**
<3.0	**12.1**	**9.06, 16.2**	**<0.001**	**5.48**	**3.84, 7.86**	**<0.001**
Hemoglobin (g/dL)						
≥12.0	REF	—		—	—	
10.0 to <12.0	**2.47**	**1.88, 3.26**	**<0.001**	**1.53**	**1.12, 2.08**	**0.007**
≤10.0	**7.8**	**6.08, 10.1**	**<0.001**	**2.17**	**1.55, 3.03**	**<0.001**

Supplemental Table 2. Univariable and multivariable logistic regression model. *Chronic medication use was defined within 1 year prior to baseline; corticosteroid use was defined within 30 days of baseline. In all cases the population median was imputed for missing variables (Body mass index was missing for 479 participants, serum albumin was missing for 72 participants, hemoglobin was missing for 46 participants). Abbreviations $eGFR_{CRE-CYS}$ = estimated Glomerular Filtration Rate calculated using the 2021 race-free combined serum creatinine and cystatin C equation, ACEi/ARB = Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker.

748 **Supplemental Table 3. Characteristics of patients with severe eGFR discrepancy**

	Overall	Severe eGFR discrepancy
Covariates	N=1988	N=139
Age	66 (14)	68 (13)
Female Sex	965 (48.5)	60 (43.2)
Race/Ethnicity		
White	1555 (78.2)	114 (82.0)
Black	184 (9.3)	10 (7.2)
Hispanic	89 (4.5)	6 (4.3)
Asian	72 (3.6)	4 (2.9)
Other	88 (4.4)	5 (3.6)
Body Mass Index (kg/m^2)		
Underweight (<18.5)	54 (3.6)	4 (4.6)
Normal (18.5 - 24.9)	442 (29.4)	28 (32.2)
Overweight (25 - 29.9)	515 (34.2)	26 (29.9)
Obese (≥30)	493 (32.8)	29 (33.3)
Comorbidities		
Hypertension	1600 (80.5)	124 (89.2)
Coronary Artery Disease	987 (49.6)	99 (71.2)
Diabetes Mellitus	1008 (50.7)	112 (80.6)
Cirrhosis	105 (5.3)	20 (14.4)
Human Immunodeficiency Virus	82 (4.1)	6 (4.3)
Smoking	806 (40.5)	67 (48.2)
Malnutrition	275 (13.8)	21 (15.1)
Medication Use		
ACEi/ARB	1128 (56.7)	77 (55.4)
Proton Pump Inhibitors	1291 (64.9)	115 (82.7)
Diuretics	1282 (64.5)	122 (87.8)
Labs		
Serum Creatinine (mg/dL)	1.62 (1.03)	1.56 (0.65)
Serum Albumin (g/dL)		
<3.0	297 (15.5)	77 (55.4)
3.0-3.49	187 (9.8)	27 (19.4)
3.5-3.9	280 (14.6)	20 (14.4)
≥4.0	1152 (60.1)	15 (10.8)
Blood Urea Nitrogen (mg/dL)		
≤17	501 (25.2)	4 (2.9)
17-25	526 (26.5)	6 (4.3)
25-39	482 (24.3)	30 (21.6)
>39	478 (24.1)	99 (71.2)
Hemoglobin (g/dL)		
≤10.0	597 (30.0)	111 (79.9)
10.0-11.9	505 (25.4)	18 (12.9)
≥12.0	886 (44.6)	10 (7.2)
Cancer types		
Urothelial	92 (4.6)	5 (3.6)
Brain	40 (2.0)	2 (1.4)
Breast	228 (11.5)	4 (2.9)
Gastrointestinal	177 (8.9)	11 (7.9)
Gynecologic	141 (7.1)	5 (3.6)
Head & Neck	50 (2.5)	5 (3.6)
Leukemia	129 (6.5)	21 (15.1)

Lymphoma	123 (6.2)	19 (13.7)
Melanoma	29 (1.5)	3 (2.2)
Prostate	147 (7.4)	5 (3.6)
Kidney	162 (8.1)	5 (3.6)
Sarcoma	4 (0.2)	0 (0.0)
Testicular	1 (0.1)	0 (0.0)
Thoracic	114 (5.7)	17 (12.2)
Thyroid	43 (2.2)	4 (2.9)
Skin (Other)	298 (15.0)	13 (9.4)

Supplemental Table 3. Severe eGFR discrepancy was defined as $eGFR_{CYS}$ more than 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS}$ < 30mL/min/1.73m^2. Count and percent or mean and standard deviations are shown. Body mass index was missing for 479 participants, serum albumin was missing for 72 participants, hemoglobin was missing for 46 participants. The remaining data was complete. The cohort median was imputed for missing data. Cancer type was determined by the most common cancer-related diagnosis code appearing prior to the baseline date. Abbreviations: eGFR = estimated glomerular filtration rate, ACEi/ARB = Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker.

Supplemental Table 4. Predictors of severe eGFR discrepancy

	Severe discrepancy group (N=139) Vs. Reference group (N= 1409)					
	Univariable			Multivariable		
Covariates	**OR**	**95% CI**	**p-value**	**Adj OR**	**95% CI**	**p-value**
Age (per 10 years)	**1.16**	**1.02, 1.32**	**0.031**	1.03	0.86, 1.25	0.743
Male Sex	0.83	0.58, 1.18	0.308	0.81	0.51, 1.29	0.38
White Race	1.35	0.87, 2.15	0.197	1.84	**1.06, 3.29**	**0.033**
Body mass index						
Normal weight	REF	—		—	—	
Underweight	1.52	0.43, 4.20	0.463	1.18	0.26, 4.43	0.82
Overweight	1.19	0.77, 1.89	0.446	**2.22**	**1.26, 4.01**	**0.007**
Obese	0.91	0.53, 1.57	0.743	**1.98**	**0.99, 4.00**	**0.053**
Smoking	**1.50**	**1.05, 2.12**	**0.024**	0.77	0.48, 1.21	0.26
Comorbidities						
Hypertension	**2.39**	**1.42, 4.31**	**0.002**	0.62	0.28, 1.40	0.24
Coronary Artery Disease	**3.24**	**2.23, 4.80**	**<0.001**	1.14	0.66, 1.98	0.64
Diabetes Mellitus	**5.36**	**3.53, 8.42**	**<0.001**	1.71	0.98, 3.02	0.061
Cirrhosis	**5.21**	**2.92, 9.02**	**<0.001**	**2.80**	**1.31, 5.98**	**0.008**
Human Immunodeficiency Virus	0.98	0.37, 2.13	0.963			
Malnutrition	1.23	0.74, 1.97	0.406			
Thyroid disease	1.70	1.16, 2.45	0.005	1.17	0.90, 1.51	0.245
Medication Use*						
ACEi/ARB	0.99	0.70, 1.41	0.968			
Proton Pump Inhibitors	**3.15**	**2.04, 5.07**	**<0.001**	1.06	0.58, 1.98	0.85
Diuretics	**5.34**	**3.27, 9.28**	**<0.001**	1.71	0.87, 3.50	0.13
Corticosteroid use	**6.67**	**4.62, 9.64**	**<0.001**	**2.38**	**1.49, 3.80**	**<0.001**
Baseline Labs						
$eGFR_{CRE-CYS}$	0.95	0.94, 0.96	**<0.001**	0.98	0.97, 0.99	**<0.001**
Albumin (g/dL)						
≥4.0	REF	—		—	—	
3.0-3.9	**12.7**	**7.13, 23.7**	**<0.001**	**3.91**	**2.00, 7.96**	**<0.001**
<3.0	**54.4**	**31.0, 102**	**<0.001**	**12.3**	**6.14, 26.0**	**<0.001**
Hemoglobin (g/dL)						
≥12.0	REF	—		—	—	
10.0-11.9	**3.77**	**1.76, 8.57**	**<0.001**	1.50	0.64, 3.78	0.36
≤10.0	**31.3**	**17.0, 64.6**	**<0.001**	**3.59**	**1.64, 8.44**	**<0.001**

Supplemental Table 4. Univariable and multivariable logistic regression model for severe group defined as $eGFR_{CYS}$ more than 50% lower than $eGFR_{CRE}$ and $eGFR_{CYS}$ <30 ml/min/1.73m^2. *Chronic medication use was defined within 1 year prior to baseline; corticosteroid use was defined within 30 days of baseline. Abbreviations: $eGFR_{CRE-CYS}$ = estimated Glomerular Filtration Rate calculated using the 2021 race-free combined serum creatinine and cystatin C equation, ACEi/ARB = Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker.

802 **Supplemental Table 5. Predictors of Vancomycin level > 30µg/dL**

	Predictors of Vancomycin level > 30µg/dL(N=55) Vs. <30µg/dL (N=227)					
	Univariable			Multivariable		
Covariates	**OR**	**95% CI**	**p-value**	**Adj OR**	**95% CI**	**p-value**
Age (per 10 years)	**0.79**	**0.65, 0.97**	**0.023**	**0.73**	**0.57, 0.93**	**0.010**
Male Sex	1.32	0.73, 2.38	0.36	1.47	0.64, 3.73	0.39
White Race	1.54	0.71, 3.72	0.30	1.38	0.61, 3.48	0.460
eGFR discrepancy	**2.89**	**1.40, 6.58**	**0.006**	**2.30**	**1.05, 5.51**	**0.047**
Body mass index	1.04	0.99, 1.09	0.096	1.04	0.98, 1.09	0.18
Smoking	0.91	0.50, 1.64	0.75			
Comorbidities						
Hypertension	1.41	0.60, 3.90	0.47			
Coronary Artery Disease	1.27	0.67, 2.56	0.48			
Diabetes Mellitus	**3.28**	**1.36, 9.77**	**0.016**	2.38	0.91, 7.47	0.098
Cirrhosis	0.94	0.36, 2.16	0.89			
Malnutrition	0.49	0.14, 1.30	0.19			
Thyroid disease	0.86	0.44, 1.63	0.66			
Medication Use*						
ACEi/ARB	0.96	0.53, 1.74	0.90			
Proton Pump Inhibitors	1.27	0.53, 3.51	0.62			
Diuretics	1.76	0.76, 4.83	0.22			
Corticosteroids	**3.51**	**1.86, 7.03**	**<0.001**	**2.91**	**1.47, 6.02**	**0.0030**
Baseline Labs						
$eGFR_{CRE-CYS}$	0.99	0.98, 1.00	0.043	0.99	0.97, 1.00	0.032
Albumin (g/dL)						
≥4.0	-	-	-			
3.0 to <4.0	2.73	0.72, 17.9	0.20			
<3.0	3.05	0.85, 19.6	0.14			
Hemoglobin (g/dL)						
≥12.0	-	-	-			
10.0 to <12.0	2.57	0.40, 50.4	0.40			
≤10.0	5.05	1.00, 92.1	0.12			

803
804 Supplemental Table 5. Univariable and multivariable logistic regression model predicting Vancomycin
805 trough level > 30 µg/dL. eGFR discrepancy defined as $eGFR_{CYS}$ > 30% lower than $eGFR_{CRE}$.
806 Abbreviations: $eGFR_{CRE-CYS}$ = estimated Glomerular Filtration Rate calculated using the 2021 race-free
807 combined serum creatinine and cystatin C equation, ACEi/ARB = Angiotensin Converting Enzyme
808 Inhibitor/Angiotensin Receptor Blocker.
809

Supplemental Table 6. Deidentified case summaries of clinical digoxin toxicity

65-70-year-old woman with atrial fibrillation and congestive heart failure	Admitted for hypercalcemia due to refractory multiple myeloma. She developed bradycardia with AV block, altered mental status, and hyperkalemia while on digoxin 0.25 mg daily, and her digoxin trough level was 3.8 ng/mL She was treated with digoxin immune fab followed by improvement in bradycardia and mental status. Digoxin was permanently discontinued.
60-65-year-old woman with metastatic neuroendocrine cancer and carcinoid heart disease	Admitted for pulmonic and tricuspid valve replacement surgery and developed recurrent atrial flutter during a prolonged hospital stay. She was treated with digoxin load (0.25mg intravenous for 3 doses) followed by maintenance digoxin 0.125mg oral daily. On hospital day 83, she developed nausea and vomiting attributed to elevated digoxin (trough level was 2.1 ng/mL) and her symptoms fully resolved with discontinuation of digoxin.

Supplemental Table 7. Predictors of 30-day mortality

	30-day mortality					
	Univariable			Multivariable		
Covariates	**HR**	**95% CI**	**p-value**	**Adj HR**	**95% CI**	**p-value**
Age (per 10 years)	1.01	0.89, 1.14	0.93	1.04	0.90, 1.18	0.614
Male Sex	0.80	0.56, 1.13	0.20	1.22	0.85, 1.75	0.28
White Race	1.60	0.99, 2.57	0.054	**1.71**	**1.04, 2.79**	**0.034**
Body mass index						
Normal (18.5 - 24.9)	REF	—		—	—	
Under weight (<18.5)	1.20	0.47, 3.07	0.70	0.97	0.37, 2.53	0.96
Overweight (25 - 29.9)	0.96	0.64, 1.44	0.84	1.06	0.69, 1.62	0.80
Obese (≥ 30)	**0.57**	**0.33, 0.98**	**0.041**	1.15	0.66, 2.00	0.62
eGFR discrepancy	**7.57**	**5.12, 11.2**	**<0.001**	**1.97**	**1.29, 3.01**	**0.002**
Smoking	1.22	0.86, 1.71	0.26			
Comorbidities						
Hypertension	0.86	0.57, 1.31	0.49			
Coronary Artery Disease	2.10	1.46, 3.03	**<0.001**	0.99	0.66, 1.51	0.98
Diabetes Mellitus	2.46	1.68, 3.60	**<0.001**	1.03	0.67, 1.59	0.89
Cirrhosis	2.70	1.62, 4.49	**<0.001**	1.11	0.64, 1.93	0.70
Human Immunodeficiency Virus	1.11	0.49, 2.53	0.80			
Malnutrition	0.61	0.34, 1.11	0.11			
Thyroid disease	1.27	0.87, 1.83	0.21			
Medication Use*						
ACEi/ARB	**0.71**	**0.50, 1.00**	**0.049**	0.90	0.60, 1.34	0.59
Proton Pump Inhibitors	**2.18**	**1.42, 3.35**	**<0.001**	1.20	0.74, 1.94	0.47
Diuretics	**2.00**	**1.32, 3.04**	**0.001**	0.67	0.40, 1.11	0.12
Corticosteroids	**5.02**	**3.56, 7.07**	**<0.001**	**1.58**	**1.09, 2.30**	**0.017**
Baseline Labs						
$eGFR_{CRE-CYS}$	**0.98**	**0.97, 0.99**	**<0.001**	**0.99**	**0.98, 1.00**	**0.027**
Albumin (g/dL)						
≥4.0	REF	—		—	—	
3.0 to <4.0	**16.3**	**6.32, 42.0**	**<0.001**	**7.17**	**2.62, 19.6**	**<0.001**
<3.0	**96.3**	**39.2, 237**	**<0.001**	**31.8**	**11.8, 86.2**	**<0.001**
Hemoglobin (g/dL)						
≥12.0	REF	—		—	—	
10.0 to <12.0	**6.10**	**2.45, 15.2**	**<0.001**	2.00	0.77, 5.22	0.15
≤10.0	**28.8**	**12.6, 65.5**	**<0.001**	**2.93**	**1.18, 7.25**	**0.020**

Supplemental Table 7. Univariable and multivariable Cox model for 30-day mortality. eGFR discrepancy defined as $eGFR_{CYS}$ > 30% lower than $eGFR_{CRE}$. *Chronic medication use was defined within 1 year prior to baseline; corticosteroid use was defined within 30 days of baseline. In all cases the population median was imputed for missing variables (body mass index was missing for 479 participants, serum albumin was missing for 72 participants, hemoglobin was missing for 46 participants). Abbreviations: $eGFR_{CRE-CYS}$ = estimated Glomerular Filtration Rate calculated using the 2021 race-free combined serum creatinine and cystatin C equation, ACEi/ARB = Angiotensin Converting Enzyme Inhibitor/Angiotensin Receptor Blocker.